

A STUDY TO DETERMINE THE ASSOCIATION BETWEEN PATTERN OF
CALCIFICATION IN CT SCAN AND STAGING OF RETINOBLASTOMA IN HOSPITAL
UNIVERSITY SCIENCE MALAYSIA (HUSM).

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Introduction: Retinoblastoma is one of the most common intraocular malignancy in children under 15 years old. About 80% of cases occurs in patients under 3 years old. The incidence varies form countries to countries. In United States of America, it occurs in 1 of every 15000 live birth. Most incidence of retinoblastoma is unilateral, bilateral involvement is seen in approximately 30% of cases and it is detected earlier. Physical and radiological examination helps in diagnosing retinoblastoma. CT scan of the orbit is one of the important tools in diagnosing retinoblastoma. Intraocular calcification can be detected in about 80% of the CT scan of orbit. Many researches have been performed since 1980s to determine association between intraocular calcification in retinoblastoma with prognosis and size of the tumour.

Objectives: To determine frequency of intraocular calcification in retinoblastoma and association between the pattern of calcification with histopathological examination, clinical data and staging.

Patients and methods: This was a retrospective descriptive study. All patients had undergone pretreatment CT scan of the orbit and enucleation. Characteristic of calcification on CT scan images which were presence of calcification, size, site and Hounsfield Unit of calcification were recorded. CT scan images were reviewed via GE Centricity PACS- IW (Integrated web) version 3.71. Histological findings which were presence of calcification, size, site of tumour and optic nerve involvement were recorded. History of presenting illness, family history, demographic data and clinical classification were sought from medical record and recorded. Association between characteristic of calcification and histological findings, clinical data and staging were determined.

Results: There was 95% intraocular CT calcification seen in retinoblastoma in this study. There was significant association between presence of calcification on CT and presence of calcification on HPE($p=0.042$). There was also significant association between presence of HPE calcification and CT calcification site($p=0.016$). Significant association noted between CT calcification size and strabismus($p=0.035$). However, there was no significant association between the patterns of calcification on CT with staging of retinoblastoma.

Conclusion: Although presence of calcification on CT scan was used as a criteria to diagnosed retinoblastoma, there is no significant association between patterns of the calcification with staging in retinoblastoma.

Prof Madya Noreen Nurfaraheen Lee Abdullah: Supervisor

1. INTRODUCTION

Retinoblastoma is one of the most common intraocular malignancy in children and one of commonest in infancy. It accounts for more than 80% of all primary intraocular tumour in children up to 15 years old (Mahoney et al. 1990). The incidence varies from countries to countries. In United State of America, it accounts in 1 of every 15000 live birth. 200 cases are diagnosed per year in the United States. The average age at diagnosis is 18 months with 80% of cases occurring before 3 years old. Approximately 30% are bilateral and are typically diagnosed earlier than unilateral cases (S.C.Kaste et al. 2000).

Main clinical presentation is leukocoria which can be seen in almost 60% of cases. Other sign of retinoblastoma is strabismus or squint which is present in 20% of cases. It has a good prognosis and a fair chance of preservation of the vision (Balmer and Munier, 2002). Other signs include atypical features that account of 20% of cases including inflammation such as inflammation of the eyes, proptosis and eye discharge. These are late sign and carry poorer prognosis.

Direct funduscopy is the first clinical examination done by ophthalmologist. It is stated that direct funduscopy with proper pupil dilatation can improved ability to observe leukocoria resulting from small retinoblastoma lesions in the posterior pole and larger lesions located outside of the posterior pole (John C. Canzano and James T. Handa,1999). Orbital sonography help in delinating good intraocular detail and provide sequential study. Retinoblastoma appears as an echogenic soft-tissue mass with various degrees of calcification. CT detects intraocular, extraocular, and intracranial disease extension. It

provide great delineation of bony abnormalities and tumoural calcifications. MRI helps the characterization of complex structure depiction of ocular, orbital, and intracranial abnormality.

It is important to detect the tumour early since it can be treated effectively with a survival rate of 90% with current treatment (Balmer and Munier, 2002). Treatment depends on the ocular status of the disease (Constantino Sábado Álvarez et al. 2005). Enucleation is still a mainstay treatment for large tumor that requires an aggressive approach especially in unilateral retinoblastoma where the vision of the eye is severed. Other treatment includes, brachytherapy, chemotherapy and external beam therapy.

The Reese – Ellsworth classification has been since the 1960s the most popular grouping system. It was devised to evaluate the response to external beam radiotherapy. New classifications are being developed as is the case of the International Classification of Retinoblastoma (Salvadore Alvarez et al. 2005) which is more concentrated on chemotherapy regime.

For our study, we would like to see association between calcification patterns with the histopathological findings and clinical data. Tumour calcification was seen much more common in tumour confined to the globe and therefore may be a favourable diagnosis for retinoblastoma (Alan Danziger et al. 1979). Degree of calcification appeared to depend upon tumour size. Only small tumours were devoid of calcification. This correlate with the theory that DNA released from necrotic retinoblastoma tumour cell has propensity to form a DNA calcium complex (Mafee et al. 2005). Hence, it is important to study the depicted pattern of calcification in relation to the histopathology to determine that some pattern of calcification represent the degree of malignancy in retinoblastoma.

SECTION TWO: LITERATURE REVIEW:

2.1 Epidemiology of retinoblastoma

Retinoblastoma is the most common malignancy of the retina in childhood. Although it is a rare disease, it accounts for 80% of all primary ocular malignancies in children up to 15 years of age (Mahoney et al. 1990) and 5% of malignant solid tumors in children (Shah et al. 2000). It is estimated that 1 case of retinoblastoma per 18,000-30,000 live births, depending on the country. In developed countries, retinoblastoma are detected early. This may be due to the good screening system in patient with family history and well educated parents. Where as in developing and underdeveloped countries, retinoblastoma is often detected late after it has invaded the orbit or brain (Bunin and Orjuela, 2007).

For eg, in England about 1/30000 live birth, 1/18000 live birth in United State and 1/16000 in Finland. In Riyadh, Saudi Arabia the incidence reported as high as 1/ 11580 (H. Olivecrona et al. 1994).

Retinoblastoma may develop in utero and up to 4 years of age. First signs appear at a median age of 7 months in bilateral cases and 24 months in unilateral cases (Aubin et al. 2002)

2.2 HISTORY OF RETINOBLASTOMA:

It is first described by Dr Peter Pawius Dutch who is an anatomist and botanist, in an autopsy report in 1597 in Amsterdam who made the discovery of tumour resembling retinoblastoma. In 1836, Langenbech, Robin, and Nystin of Paris confirmed by pathological studies that the tumor microscopically arising from the retina. Retinoblastoma

was first described as a specific entity by James Wardrop in 1809, with enucleation as his suggested treatment. Histologic studies including those of Flexner and Verhoeff and subsequent electron microscopy have given insights into its pathogenesis. Wintersteiner reported the resemblance of the tumor rosettes to photoreceptors of the adult retina. (Albert DM, 1987). In the 1920s, Verhoeff believed that the tumor arose from embryonic retinal cells and proposed the name retinoblastoma.

2.3 SECONDARY PRIMARY MALIGNANCIES

Persons with bilateral retinoblastoma are at higher risk of developing second primary malignancies throughout life. The cumulative incidence of second cancer 50 years after diagnosis is 51%. The mean latency between retinoblastoma and second malignancy is approximately 13 years. External-beam radiation increases the risk of second malignancy and shows a radiation dose-response relationship for all sarcomas. Most second malignancies are high-grade tumors and having poor prognosis. Osteogenic sarcoma, the most common second tumor, often arises due to radiation. Other reported cases of malignancies include neuroblastoma, chondrosarcoma, rhabdomyosarcoma, glioma, leukemia, sebaceous carcinoma, squamous cell carcinoma, and cutaneous melanoma (Smith and Donaldson, 1991).

2.4 RISK FACTORS

Genetic factor has been found as one of the precursor for retinoblastoma. Alfred Knudson formed his famous ‘two hit’ hypothesis of tumor suppression. He studied inherited and

noninherited retinoblastoma cases. He proposed that inherited children with retinoblastoma must be borned with mutation or one hit, already in the germline and later on only required a second tumour activating hit to formally formed retinoblastoma. In patients with nonheritable form of retinoblastoma, the first hit comes later on after the patient was borned in already differentiated retinal cells. Once hit cells accumulates a second hit later in childhood and explain why the presence of retinoblastoma later on in children with non heritable form of retinoblastoma (P.H. Fitzgerald et al. 1983). In inheritable cases, mutation of the tumor-suppressor gene *RB1* responsible for retinoblastoma also increases the risk of neuroectodermal lesions and other primary nonocular tumors.

Patients who inherited an *RB1* mutation would develop tumors earlier, and they would often develop more than one tumor. In contrast, individuals who did not inherit a mutation would almost always be affected by a single tumor. This statement, which Knudson called the two-mutation hypothesis, is now known as the two-hit hypothesis. Based on the predicted mutation rate, Knudson expected that many individuals in the general population would acquire a single somatic mutation in the *RB1* gene over their lifetime, and that the retinas of most people would therefore likely contain small groups of retinoblasts that had received one "hit" in the *RB1* gene. In order to become cancerous, each retinoblast with one mutant copy of the *RB1* gene would need to acquire a mutation in the remaining wild-type copy of the gene. Most individuals who had one hit did not develop retinoblastoma, however, because most of their mutated cells had already differentiated and quit dividing before they could receive a second hit (Heidi Chial, 2008).

Other nonheritable factors that are concern with risks of retinoblastoma are poor living conditions, maternal diet deficiency, and human papilloma virus infections. Some regional variations may be linked to genetic environmental susceptibility or specific population behavioral patterns. In vitro fertilization has been reported as an increased risk of retinoblastoma (Moll et al. 2003). There is no reported predilection concerning sex or race.

2.5 PATHOLOGY

Most retinoblastomas are composed of undifferentiated cells with hyperchromatic nuclei and very scant cytoplasm. The mitotic rate is high and tumors often outgrow their blood supply, resulting in patches of necrosis 100 to 200 microns from nutrient vessels. The most important prognostic finding is the status of the optic nerve. The depth and extent of tumor invasion of the nerve strongly correlate with survival. Tumor present at the surgical margin of the optic nerve or tumor infiltration of the subarachnoid space has a poor prognosis. Focal signs of retinal differentiation (eg, tumor rosettes and fleurettes) are common but have little prognostic importance.

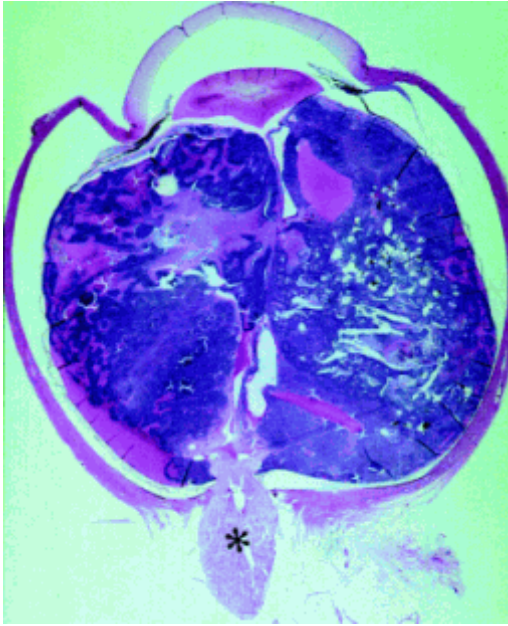


Figure 2.1 Histologic section of an eye filled with retinoblastoma. Multiple section of the optic nerve(*) showed no evidence of tumour involvement. (Adapted from [http.www.moffit.org](http://www.moffit.org).)

2.6 PATHOPHYSIOLOGY

The clinical features of retinoblastoma varies according to the tumor growth pattern and duration, degree of vascularization, presence of calcifications, vitreous seeding, retinal detachment or hemorrhage. Vitreous and subretinal seedings are the characteristic clinical signs of advanced endo- or exophytic retinoblastoma. Retinoblastoma arising from the developing neuroretina, and it shows three variants of tumor growth which are endophytic, exophytic and diffuse infiltrating. A tumor may display both endo- and exophytic features, in which cases it is considered a mixed growth pattern (S. C. Kaste, 2000).

2.6.1 Endophytic

It occurs when the tumour growth breaks through the internal limiting membrane and a whitish mass, either showing an absence of tumor vessels or showing minute but irregular vessels, becomes visible. This growth pattern is characteristic of vitreous seeding in which tissue fragments become separated from the main tumor. Endophytic form manifests as one or more isolated or coalesced tumors of variable size, round or oval-shaped, yellowish-white (calcifications) or pinkish (vascularized) in color, with a marked tendency to vitreous seeding. In some aggressive cases tumor cells, resembling spheroid masses, may be seen floating in the vitreous and anterior chamber. These floating masses may obscure the view of the primary mass.

2.6.2 Exophytic

This growth pattern occurs in the subretinal space (behind the retinal layer) and is associated with the accumulation of subretinal fluid and retinal detachment. The tumor cells may enter the choroid layer of the eye and then infiltrate blood vessels or ciliary nerves. Retinal detachment will cause masking of the underlying tumors, and secondary seeding in the subretinal space.

2.6.3 Diffuse infiltrating

This is a rare subtype which makes up for 1.5% of all the cases of retinoblastoma. Here, a distinct tumor mass is absent although tumor cells infiltrate the retina. Diffuse infiltrating retinoblastoma is a progressive lesion, often of greyish plaque-like appearance, that may progressively infiltrate the anterior segment and lead to sedimentation of tumoral cells in

the anterior chamber (pseudohypopyon). At this stage, the clinical appearance mimics that of severe inflammation. No obvious calcification seen.

2.7 ANATOMY OF EYE

Anatomy of orbit can be divided into several areas which include bony orbit, globe intraconal, conal and extraconal compartment. The medial wall is formed mostly by the ethmoid bone. Anterior to this is the lacrimal bone and part of the horizontal portion of the frontal bone. Posterior to this is the maxillary bone and the lesser wing of the sphenoid. The lateral wall is formed mostly by the greater wing of the sphenoid. Anterior to this is the orbital surface of the zygomatic bone, and a small contribution again from part of the horizontal portion of the frontal bone. The superior wall is formed mostly by the orbital surface of the frontal bone. The inferior wall is formed mostly by the maxillary bone.

The globe is mostly fluid filled and is surrounded by three major lining which are sclera, uveal tract (choroid, iris and ciliary body) and the retina. The lens and iris divide the globe cavity into an anterior chamber filled with aqueous humor, and a posterior chamber filled with vitreous humor. The optic nerve can be traced out from its intraorbital part to the intracranial part. It measures about 5 cm long and is divided into four segments which are intra-ocular, intra-orbital, intracanalicular and intracranial. The subarachnoid space between the dura and pia covering the optic nerve is continuous with that of the suprasellar cistern. There are six extra-ocular muscles, including four rectus muscles and two oblique muscles. These include superior, inferior, medial and lateral rectus muscle and superior and inferior oblique muscle. Thick fascial layers, collectively termed the orbital septum,

situated anterior to the globe divide the more anterior skin and subcutaneous tissues to preseptal compartment from postseptal compartment.

Arterial supply to orbit is mainly via the three large terminal branches of the ophthalmic artery, which are lacrimal, nasociliary and frontal branches, in addition to smaller branches, mainly the central artery of the retina which supplies the inner aspect of the optic nerve and short and long ciliary branches. Veins in the orbit tend to follow arteries but demonstrate greater interconnections until they form the superior ophthalmic vein, which drains through the superior orbital fissure into the cavernous sinus, and the inferior ophthalmic vein, which drains through the inferior orbital fissure to the cavernous sinus and the pterygoid plexus.(Grainger Allison et al, 2008)

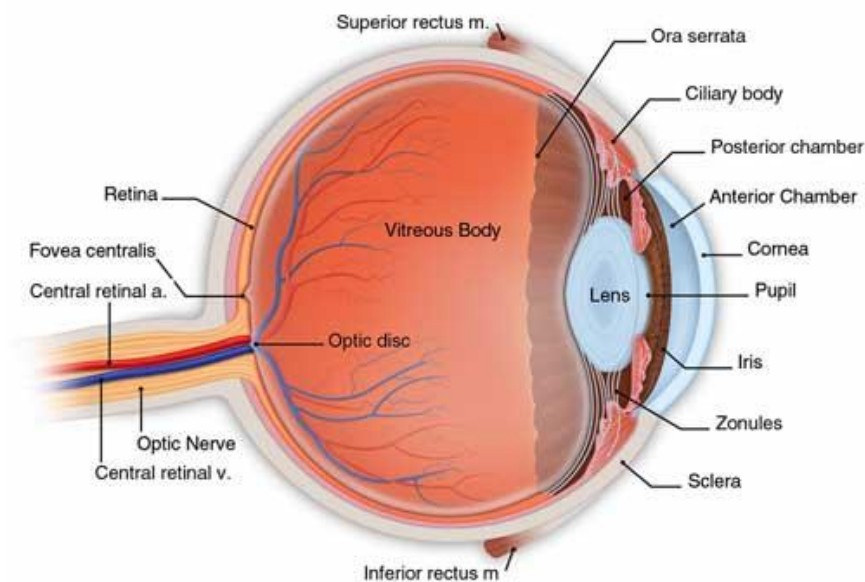


Figure 2.2 Gross anatomy of the eye. (Adapted from <http://www.eyesandeyesight.com/2009/02/anatomy-of-the-eye>)

2.8 FUNCTION OF RETINA

Retina is a light-sensitive tissue lining the inner surface of the eye. The optics of the eye create an image on the retina, which serves much the same function as the film in a camera. Light striking the retina initiates a cascade of chemical and electrical events that ultimately trigger nerve impulses. These are sent to various visual centers of the brain through the fibers of the optic nerve.

The retina is a complex, layered structure with several layers of neurons interconnected by synapses. The only neurons that are directly sensitive to light are the photoreceptor cells. These are mainly of two types: the rods and cones. Rods function mainly in dim light and provide black-and-white vision, while cones support daytime vision and the perception of colours. A third, much rarer type of photoreceptor, the photosensitive ganglion cell, is important for reflexive responses to bright daylight.

Neural signals from the rods and cones undergo complex processing by other neurons of the retina. The output takes the form of action potentials in retinal ganglion cells whose axons form the optic nerve. Several important features of visual perception can be traced to the retinal encoding and processing of light.

2.9 PRESENTING SYMPTOMS

The primary sign is leukocoria in 60% of cases. It is also known as cat reflex or white papillary reflex. It is indicative of reflection of light from a tumoural lesion within the

pupillary area when the fundus is directly illuminated. This white pupillary reflex is commonly seen on flash photography or torch by the light. Initially it is intermittent, depending on the lighting, degree of pupil dilation, direction of gaze, angle of observation and, most importantly the location and size of the tumor. Other differential diagnosis for leukocoria are The two most frequent are Coats' disease and persistent hyperplastic primary vitreous (PHPV), followed by ocular toxocariasis.

Second most important sign of retinoblastoma is strabismus which can be found in about 20% of cases. It is caused by the tumour growth that extends to the macula and caused difficulty in seeing the object. In other word, strabismus is an invaluable early sign carrying an excellent prognosis and a good chance of eye preservation.

Other sign of retinoblastoma are atypical and can be manifested as inflammatory reaction in about 20 %. These include redness, swelling and proptosis of the eye. These are late signs and it usually indicate that the eye has loss its function. Prognosis is also poor if there is development of these symptoms.



Figure 2.3 Advanced intraocular retinoblastoma present as bilateral leukocoria and strabismus. (Adapted from en.wikipedia available from: <http://Wikipedia.com>)

2.10 EXAMINATIONS

Diagnosis of retinoblastoma can be made on indirect ophthalmoscopy in about 90% of cases. Pupillary dilation is an excellent tool that help to increased the ability of the examiner to detect leukocoria (John C. Canzano and James T. Handa, 1999). Early lesions appear as flat, transparent, or slightly white placoid tumors in the neurosensory retina. As tumors enlarge, they have a white color with chalky, fleck- like deposits of calcium.

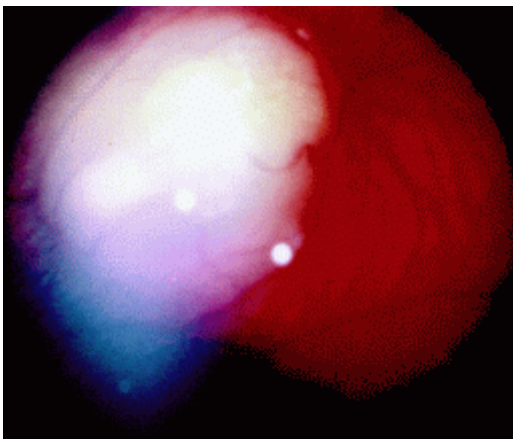


Figure 2.4 Fundus of the left eye revealing a small retinoblastoma just outside the posterior pole with early calcification. Available from: H. Lee Moffitt Cancer Center & Research Institute web site)

2.10 RADIOLOGICAL EXAMINATION

2.10.1 Ultrasound of the orbit

Orbital sonography provides good intraocular detail and allows sequential study without ionizing radiation. It is also cost effective and rapid investigation. The prerequisite

for HRSG is high frequency transducers ranging from 5- 15 MHz with short focus. No specific preparation or sedation is required. The mobility of sonographic equipment is advantageous for intraoperative imaging performed in conjunction with ophthalmologic examination. Warm sterile gel is applied to a closed eyelid. Transducer was put on to the eye and light pressure is used. Excessive ocular pressure can cause bradycardia and induce pain. Color and power Doppler capability, power up to -3 dB was used. Transverse and longitudinal planes provide excellent tumor detail. Retinoblastoma appears as an echogenic soft-tissue mass with various degrees of calcification. Tumors tend to outgrow their blood supply resulting in areas of necrosis within the tumour. The vitreous may have echogenic debris from hemorrhage, increased globulin content, or tumor seeding. However, this technique is limited to study of the globe and anterior orbit, if there is intraocular calcification, the area posterior to it cannot be assessed due to hampered ultrasound wave signal, and is degraded by patient motion. It is recommended that routine clinical screening of all parents and sibling of retinoblastoma patient to provide earlier detection of retinoblastoma and treatment at presymptomatic disease stage.

2.10.2 CT scan orbit.

CT detects intraocular, extraocular, and intracranial disease extension. It provide great delineation of bony abnormalities and tumoural calcifications. Calcification is one of the most important findings in diagnosing retinoblastoma. A lesion with calcification within an orbit is which is seen in children younger than 3 years old is highly suspicious of retinoblastoma. Calcification in retinoblastoma is seen in almost 80% of cases. However,

delineation of intraocular soft-tissue detail is limited with CT. Contrast enhancement is typically used but may obscure underlying calcifications unless preceded by a nonenhanced study. On CT, retinoblastoma is characterized by enhancing intermediate-density soft-tissue mass or masses, with varying degrees of calcification, calcification increases with therapeutic response. The vitreous may be abnormally dense from debris, hemorrhage, or increased globulin content.

Calcification which is present in up to 95% on can be readily demonstrated on CT which can help to improve the diagnosis of retinoblastoma and prevent misdiagnosis where unnecessary enucleation is performed (T R hedges III et al, 1982).



Figure 2.5 Left retinoblastoma with dense nodular intraocular calcification.

2.10.3 MRI of the orbit.

MRI helps the characterization of complex structure depiction of ocular, orbital, and intracranial abnormality, thus introducing an additional level of differential criteria. The multiplanar capabilities of MR imaging provide detailed examination of tumors and retrobulbar and intracranial structure. Retinoblastoma is a heterogeneously enhancing soft-tissue mass with various degrees of calcification on MR imaging. Lesions are typically hyperintense to vitreous on T1- weighted sequences and hypointense to vitreous on T2-weighted sequences. The vitreous may be abnormally bright on T1-weighted sequences because of increased globulin content and a decreased ratio of albumin to globulin that occurs with malignancy. Calcifications and lesions smaller than 2 mm are unreliably revealed with MR imaging.



Figure 2.6 Left retinoblastoma with hypointense area in all sequence seen within suggestive of calcification.

2.11. CLASSIFICATION OF RETINOBLASTOMA.

Several staging has been developed to assist in management of the retinoblastoma. Previously retinoblastoma was staged according to Reese Ellsworth staging system. The Reese – Ellsworth classification has been devised in 1960s. It was devised to evaluate the response to external beam radiotherapy (EBRT).

TABLE 2.1 **Reese – Ellsworth Classification for conservative treatment of retinoblastoma** (Constantino Sábado Álvarez et al. 2005).

Group I: Very favourable	(a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator (b) Multiple tumors, none over 4 disc diameters in size, all at or behind the equator
Group II: Favorable	(a) Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator (b) Multiple tumors, 4 to 10 disc diameters in size, behind the equator
Group III: Doubtful	(a) Any lesion anterior to the equator (b) Solitary tumors larger than 10 disc diameters behind the equator

Group IV: Unfavorable	(a) Multiple tumors, some larger than 10 disc diameters (b) Any lesion extending anterior to the ora serrata
Group V: Very unfavourable	(a) Massive tumors involving over half the retina (b) Vitreous seeding

New classifications are being developed as is the case of the International classification of Retinoblastoma which was proposed by Abela et al (2005). The high successes of the new modalities in the management of retinoblastoma reputed the clinicians the difficulties in applying the previously used Reese-Ellsworth classification for conservative treatment of retinoblastoma.

Several methods of classification have been developed for intraocular retinoblastoma, and the more recent is the International Classification of Retinoblastoma (ICRB). The current ICRB is very useful in guiding the treating clinician to choose the most appropriate treatment methods and might assist the prediction of the chemoreduction and focal treatment methods.

Table 2.2 Grouping system for eyes in International Classification of Retinoblastoma Board.

Group	Criteria
A – very low risk Tumors 3 mm or smaller	Small round tumor(s) located away from the fovea and disc

	<p>≥ 3 mm from the fovea</p> <p>≥ 1.5 mm from the optic disc</p> <p>No vitreous seeding</p> <p>No vitreous seeding</p>
<p>Group B – low risk</p> <p>All eyes without tumor dissemination not in Group A</p> <p>Tumor dissemination is defined to include vitreous seeding and the presence of subretinal fluid, even if subretinal seeding is not clinically apparent</p>	<p>Any size, shape or location</p> <p>No vitreous or subretinal seeding</p>
<p>Group C – moderate risk</p> <p>Eyes with only local tumor dissemination</p>	<p>Vitreous or subretinal seeding no more than 3 mm from tumor</p>
<p>Group D – high risk</p> <p>Eyes with diffuse tumor dissemination endophytic or exophytic disease.</p>	<p>Vitreous seeding large, diffuse and/or greasy</p> <p>Avascular masses of tumor may be present in the vitreous</p> <p>Subretinal dissemination may consist of fine seeds, large avascular plaques on the underneath of the detached retina, or extensive subretinal masses (exophytic disease)</p>

Group E – very high risk eyes	Neovascular glaucoma
Unsalvageable eyes	Massive intraocular hemorrhage
	Blood-stained cornea
	Massive tumor necrosis associated with aseptic orbital cellulitis
	Phthisis or prephthisis
	Tumor anterior to anterior vitreous face
	Anterior segment tumor
	Tumor touching the lens
	Diffuse infiltrating retinoblastoma

2.12 Treatment:

The primary goal of retinoblastoma therapy is to save life and preserve useful vision, and thus needs to be individualized. Factors that need to be considered include unilaterality or bilaterality of the disease, potential for vision, and intraocular and extraocular staging. Retinoblastoma rarely metastasizes, and the chance of cure remains excellent (C. Rodriguez-Galindo, 2010). There are multidisciplinary approach in treating retinoblastoma involving the oncologist, ophthalmologist and radiologist team to make sure that prompt and appropriate treatment can be given.

Standard treatments for retinoblastoma have yielded excellent results when measured in terms of survival and preservation of vision. With conventional therapies, survival exceeds 90%. Standard therapy for unilateral retinoblastoma has traditionally been

enucleation. For bilateral retinoblastoma, enucleation of the more advanced eye and external-beam radiotherapy for the less affected eye have been standard therapies. Over the last few decades, this general approach has witnessed an expanding role of eye-salvaging therapy, particularly external-beam radiation for medium-sized tumors and radioplaque therapy for smaller tumors. Some small tumors can be destroyed with cryotherapy or laser, depending on their location and thickness.

Despite the excellent cure rates, there are several drawbacks to the current arsenal of therapies. Enucleation sacrifices all vision and causes some degree of cosmetic deformity. External-beam radiotherapy is highly effective in destroying most tumors that fill less than half the eye, but failure rates increase with more advanced tumors. Most importantly, nearly 51% of patients with heritable retinoblastoma will develop a second malignancy within five decades of radiotherapy. These undesirable risks and outcomes have prompted a search for alternative therapies to salvage eyes and avoid the risk of radiotherapy.

Chemotherapy has been historically regarded as ineffective for intraocular retinoblastoma, and its use has been restricted to treatment of extraocular disease. Pilot studies using drug regimens that may cross the blood-ocular barrier combined with supplemental laser and cryotherapy have reported favorable results.

2.12.1 External beam Radiotherapy

If retinoblastoma is multifocal, close to the macula or optic nerve, and vision is well preserved, It is inadequate to apply only cryotherapy, photocoagulation, or plaque

therapy as a monotherapy. Enucleation is too aggressive since the vision is still preserved. For these cases, the usage of external-beam irradiation or chemotherapy with focal therapy is recommended. External- beam radiation therapy and chemotherapy are also indicated for large tumors and vitreous seeding. The treatment for external beam therapy was documented in 1910, when Hilgartner reported that treatment of a case of bilateral retinoblastoma with X-rays in 1910. This has encouraged other oncologist to further explore X- ray treatment. In 1918, Verhoeff cured a case of retinoblastoma with X-ray treatment (Marcus et al. 1990).

2.12.2 Chemotherapy

Chemotherapy has been used for many years in the treatment of extended retinoblastoma, to treat or prevent metastatic spread. Combined chemotherapy with cyclophosphamide, doxorubicin, methotrexate and actinomycin-D, as in other embryonic neural tumors has been employed (Constantino Sábado Álvarez et al. 2005).

2.12.3 Enucleation

Enucleation is indicated for majority of the children present with a large tumor that requires an aggressive approach especially in unilateral retinoblastoma where the vision of the eye is severed. In bilateral retinoblastoma when both eyes are blind, a bilateral enucleation is done. This occur in 20-40% of cases. The optic nerve is cut near its exit from the socket to make sure that a long segment of the nerve is obtained. This is important especially when the tumour has already infiltrate the nerve to make sure that the

surgical margin is free from tumour cell. In young children, orbital growth slows after enucleation. As the child grows, the orbit appears small. For better orbit growth and cosmetic purpose, orbital prosthesis can be used to be fit within the globe.

2.13 Prognosis

Prognostic factors depend on the ocular status. The staging system for retinoblastoma must fulfill at least two requirements. First, it must predict likelihood of cure, a requirement of all malignancy staging systems. However, an important goal of retinoblastoma treatment is preservation of sight in the affected eye. Previously, the most widely used staging grouping system for retinoblastoma was proposed by Reese (1976) and Ellsworth (1969). This system does not predict survival probability. However, it predicts the chance of visual preservation with conservative therapy (Constantino Sábado Álvarez et al. 2005).

Eye enucleation and external beam radiation were the mainstays of therapy in the past but in recent years they are being displaced by combined chemotherapy followed by focal treatments as cryotherapy, phototherapy or brachytherapy with plaques. These therapeutic plan encompasses survival rates over 90%, making second cancers instead of progressive disease the most frequent cause of death nowadays in patients with hereditary retinoblastoma.

When retinoblastoma has spread outside the eye globe prognosis impairs notably and it is a great challenge to achieve complete remission especially in case of central nervous system involvement.

2.14 Genetic counseling.

The risk to the offspring of an individual with retinoblastoma depends on whether patient has a germline mutation. Risk assessment is accomplished by obtaining a family history and determining if the patient has unilateral, bilateral or multifocal tumour involvement. Parents and siblings of persons with retinoblastoma should be examined for occult retinocytoma or spontaneously regressed retinoblastoma. The presence of retinocytoma or a regressed retinoblastoma has the same genetic implications as retinoblastoma. Penetrance of RB1 mutations are high, meaning that approximately 90% of individuals with a germline RB1 mutation will develop retinoblastoma.

Laboratory techniques to identify RB1 are not routinely available. However, predictive testing for retinoblastoma has great potential for improving the effectiveness of genetic counseling by positively identifying germline mutations in persons with unilateral involvement and asymptomatic carriers (Retinoblastoma, Curtis E Margo et. al. available at <http://www.moffit.org>,) [Accessed 4/10/2010]